Remarks

Reconsideration of this application is respectfully requested.

I. Status of the Claims

Claims 12, 14, 18, and 20 have been canceled. Claims 1, 3-6, 8, 10, 11, 15, 19, 21, 23 and 24 have been amended. Upon entry of the foregoing amendments, claims 1-11, 13, 15-17, 19, 21, and 23-28 are pending, with claims 1, 19, and 21 being the independent claims.

Claims 1, 3-6, 8, 10, 11, 15, 19, 21, 23 and 24 have been amended for consistency in language and to make explicit that which was implicit in the previous version of the claims. These amendments do not narrow the scope of the claims. These amendments are believed to introduce no new matter and their entry is respectfully requested.

Based on the amendments to the claims and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

II. The Objection To Claim 20 Under 37 C.F.R. § 1.75(c) Is Moot

In the Office Action at page 2, section 4, claim 20 was objected to under 37 C.F.R. § 1.75(c) for being in improper dependent form. Claim 20 has been canceled. Applicants respectfully request withdrawal of this objection.

III. The Rejection of Claims 1-19, 21, and 23-28 Under 35 U.S.C. § 112, Second Paragraph Should Be Withdrawn

In the Office Action at pages 2 and 3, section 5, the Examiner has rejected claims 1-19, 21, and 23-28 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants respectfully request reconsideration and withdrawal of these rejections in view of the amendments to the claims.

Claims 1, 19 and 21 were rejected as allegedly being indefinite in the use of the phrase "wherein the cancer cell classification comprises terminal cells and proliferative cells" as the Examiner alleges "[i]t is unclear how a [sic] classifying a cell according to a type can comprise the cell type itself." The claims have been amended to recite "classifying said isolated cancer cells as terminal cells or proliferative cells . . . ." Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 11 was rejected as allegedly being indefinite for the use of the phrase "at least three cancer cells form a microtumor." The claim has been amended to make explicit that which is implicit. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 12 was rejected as allegedly being indefinite for lack of antecedent basis in claim 1. Claim 12 has been canceled. Applicants respectfully request withdrawal of this rejection.

Claim 14 was rejected as allegedly being indefinite in the use of the phrase "natural body fluid sample." The claim has been canceled as "body fluid sample" includes "natural body fluid sample." Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 18 was rejected as allegedly being indefinite because of the phrase "wherein cells are isolated using a circulating cancer cell test." Claim 18 has been canceled as claim 1 encompasses this embodiment. Applicants respectfully request withdrawal of this rejection.

Claim 19 was rejected as allegedly being indefinite as the Examiner alleges "it is not clear how steps (b) differ from steps (c), as step (b) recites, 'characterizing said isolated cells...to distinguish cancer cell classes' and step (c) recites 'determining the classification of cancer cells isolated.'" Claim 19 has been amended to delete step (b). Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 21 was rejected as allegedly 1) lacking an active step relating the comparison of classifications of cancer cells with the assessment of the medical procedure, and 2) reciting assessing the efficacy of a medical procedure in the preamble of the claim and assessing whether the procedure is efficient in the final method step. Accordingly, claim 21 has been amended to make explicit that which is implicit. Applicants respectfully request reconsideration and withdrawal of this rejection.

IV. The Rejections of Claims 1-21 and 23-28 Under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn

In the Office Action at pages 3 and 4, section 6, the Examiner rejected claims 1-21 and 23-28, under 35 U.S.C. § 112, first paragraph, allegedly for lack of enablement. Applicants respectfully traverse this rejection.

MPEP § 2164.04 reads, in pertinent part:

> In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *Citing In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

See also, In re Cortright, 49 USPQ2d 1464, 1466 (Fed. Cir. 1999); *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971).

This rejection was originally made in the Office Action dated May 1, 2001, and the Examiner maintained it for the reasons presented in that Office Action and in view of Wang, *et al.*, (*Cancer*, 2000, Vol. 88, pp.2787-2795, reference AS, hereinafter "Wang"). At page 4 of the Office Action, the Examiner cited a passage from Wang (p. 2795, last paragraph) and concluded:

> As this paper represents the work of the instant inventor which was submitted for publication on April 23, 1999 and the instant specification has a priority date of February 10, 1999, it is further evidence that at the time the application was filed, one of skill in the art would not be able to interpret the data obtained from the instant method of classifying cancer cells in terms of patient prognosis without undue experimentation. Further, this evidence corroborates the examiners [sic] rejection (page 3, lines 23-26) of the previous Office action which states that due to the lack of teachings in the specification regarding the link between the resulting classifications of isolated tumor cells in terms of absolute numbers and percentages and the positive diagnosis of metastatic cancer, one of skill in the art would not know how to use the instant claimed invention.

Applicants respectfully disagree. The Examiner has provided only conclusory statements that the claimed methods allegedly are not enabled. The Examiner has not provided any evidence or sound scientific reasoning why there is reason to doubt that the claimed methods are not in compliance with the enabling requirement of 35 U.S.C. § 112, first paragraph. Absent such evidence or sound scientific reasoning, this rejection is improper.

Specifically, the Examiner has not provided any evidence or sound scientific reasoning why there is reason to doubt that one of ordinary skill in the art could, after reading the

present specification, classify a cancer cell in a body fluid as either terminal or proliferative as called for by claims 1-11, 13-17, 27 and 28, determine the presence or absence of cancer cells capable of causing metastatic cancer, as called for in claims 19, 27 and 28, or determine the efficacy of a treatment, as called for in claims 21 and 23-28. The passage from Wang quoted by the Examiner has been taken out of context. The sentence preceding the quoted passage reads, "[i]n this study, large numbers of circulating prostate carcinoma cells were observed in the blood of ***a few*** patients: as many as 50-100 cells per 20 mL of blood." (Sentence bridging pages 2794 and 2795, emphasis added). The passage cited by the Examiner merely refers to further analysis of a small subset of the patients examined and does not call into question the ability of one skilled in the art to use information in the specification to practice the claimed methods.

Rejection of May 1, 2001

In addition to citing Wang, the Examiner maintains the rejection under 35 U.S.C. § 112, first paragraph, for reasons of record in the Office Action dated May 1, 2001, at section 4, pages 2-7. In the first portion of this rejection (pages 3 and 4), the Examiner asserted:

1. the specification fails to teach how to use the proposed classification system because it does not teach the relative partitioning of the intermediate cell in Figure 1B and it lacks a link between the absolute numbers and percentages of the various cell types and the diagnosis of metastatic cancer (page 3 last 6 lines);

2. the specification does not teach how to evaluate the efficacy of therapy on an individual having some number of circulating cancer cells classified

intermediate/indeterminate because of the potential of intermediate cells to enter either the terminal or proliferative pathway (page 4 lines 4-7);

3. the specification does not correlate the percentages or absolute numbers of cells classified as proliferative and/or intermediate with the likelihood of metastatic breast cancer or prostate cancer (page 4, lines 9-11);

4. the specification does not correlate changes in percentages or absolute numbers of cells classified as proliferative and/or intermediate with the efficacy of treatment (page 4 , lines 11-13); and

5. claim 21 encompasses methods where cells are isolated and compared before administration of a treatment (page 4, lines 16-20).

In regard to points 1, 3 and 4 above, claim 1 is directed to a method of isolating circulating cancer cells and classifying cancer cells in a bodily fluid sample as terminal cells or proliferative cells using cytological and morphological analyses using fluorescence microscopy. The specification provides ample teaching, including a working example, of how to classify cancer cells from a bodily fluid (see pages 21-29 and Example 2), including the markers to be used to classify the cells. The ability to classify the cancer cells as according to the method would be intrinsically valuable in monitoring a cancer patient. Claim 19 is drawn to a method of determining the presence or absence of cancer cells capable of causing metastatic cancer. The characteristics of proliferative cells are described in detail in the specification (for example, at pages 14-16) and one skilled in the art would be able to identify them using the teachings of the specification. The ability to classify cancer cells lends to determining the presence or absence of proliferative cells, which is an indication of metastatic cancer. The method of claim 21 calls for assessing the efficacy of

a treatment by comparing the classification of cells pre- and post-treatment. (Note that claim 21 was amended in the preliminary amendment of January 11, 2002, to address the timing issue raised in point 5.) The specification teaches the comparison of the cell classifications determined before and after treatment and that an increase in terminal cells indicates a positive effect from the treatment and that an increase in proliferative cells indicates a negative response to the treatment. (See, for example, page 6, lines 6-30). Claims 1, 19 and 21 do not require numerical analysis of the cells of each type classified; the claims require classifying the cancer cells as terminal or proliferative cells.

As applied to each of the claimed methods, this rejection appears to be an attempt to read a limitation into the claim that is not present in the claimed method. In view of the ample teaching in the specification regarding the isolation and classification of cells, Applicants respectfully submit that this rejection is not properly applied to the claims and respectfully request its withdrawal.

In point 2 above, the Examiner seems to be indicating that assessing the efficacy of therapy on an individual is not possible because of the potential of intermediate cells to enter either the terminal or proliferative pathway. The claims require classifying terminal or proliferative cells; the potential of intermediate cells to enter either the terminal or proliferative pathway is immaterial to the claimed method. The Examiner points to no scientific articles and provides no scientific reasoning in support of this assertion. As discussed above, the Examiner bears the initial burden of providing evidence that establishes a reasonable basis to question the enablement of the claimed invention. Applicants respectfully submit that the Examiner has failed to meet this burden. Accordingly, this rejection is improper and Applicants respectfully request its reconsideration and withdrawal.

Rejection of May 1, 2001, (A) as drawn to a terminal pathway

At pages 4 to 5 of the Office Action dated May 1, 2001, the Examiner asserted that the specification does not adequately describe the fate of cells of the type of "D" in Fig. 1 and, therefore, one skilled in the art would not know how to use the claimed method of classification of circulating cells. Applicants respectfully request reconsideration and withdrawal of this rejection.

As the Examiner acknowledged at page 5, lines 2-3, cells of type "D" are positive for apoptotic markers. The Examiner then asserted that this is not objective evidence that the cells are, in fact, apoptotic and, therefore, terminal. (Page 5, lines 4 and 5). The Examiner cites Leverrier, *et al.* (*Current Biology*, 2001, Vol. 11, pp195-199) for the proposition that the broken cells of type "F" cannot be indicative of apoptosis because "cells undergoing apoptosis in vivo do not result in the accumulation of broken cells but are removed prior to breaking up by phagocytes." Office Action of May 1, 2001, page 5, lines 6-7. The Examiner theorizes that the broken pieces actually are the result of the fragmentation of fragile cell type "C" during purification rather than apoptosis of cell type "D" and/or "E." The Examiner continues by stating: "[A]s cell 'D' is not anucleate and has not been demonstrated to undergo apoptosis, it can potentially continue to propagate, thus, there is no objective evidence for the designation of a terminal pathway." (Page 5, lines 10-12). The Examiner concludes by stating "[g]iven this lack of guidance in the specification regarding the fate of cell "D", one of skill in the art would not know how to use the claimed method of classification of circulating cells." (Page 5, lines 12-14).

As discussed above, the Examiner has the burden of providing a reasonable basis to doubt the enablement of claimed invention. In this case, Applicants identified apoptotic

markers on cells of type "D" and from that concluded that the cells are terminal and not proliferative. See, for example, page 12, lines 24-30. The Examiner does not provide any evidence in support of the assertion that the cells are not apoptotic, nor does the Examiner provide any scientific reasoning that would suggest that cells positive for apoptotic markers are anything other than apoptotic. The document cited by the Examiner does not provide any evidence in support of the view that the cells of type "D" are not apoptotic. The document cited by the Examiner concerns an *in vitro* study of bone marrow CSF-1 derived macrophages incubated with an Il-3-dependent cell line, Baf-3, that undergoes apoptosis upon growth factor starvation. See Leverrier, page 195, and Figure 1. The Examiner seems to be asserting that there can be no apoptotic cells in circulation because such cells undergo phagocytosis. The cited document does not discuss the *in vivo* presence or absence of apoptotic cells. The document does not suggest that cells displaying apoptotic markers are not apoptotic. Even if the cells of type "F" derive from fragmentation of cells of type "C," there is no suggestion in the document that cells of type "F" are anything other than terminal. Thus, the present specification teaches the classification of cells as terminal based upon the presence of markers identified in the specification and the Examiner has not provided any evidence to suggest that this classification is not correct. Applicants respectfully submit that the Examiner has not met her initial burden and, therefore, this rejection is improper and should be withdrawn.

Rejection of May 1, 2001, (B) as drawn to identification of cell types "A," "B" and "C"

At pages 5 to 6 of the Office Action dated May 1, 2001, the Examiner asserted that the specification would not have enabled one skilled in the art to classify a cell having a diameter of 10 as a fragile, large cancer cell (claim 3, page 5, lines 16-19) and would not

have enabled one skilled in the art to identify a cell having a diameter of 10-20 μm as a proliferative cell (Claim 9, page 6, lines 2-3). The Examiner further asserts that the specification would not have enabled one skilled in the art to distinguish between cells of type "A" and cells of type "B." (Page 6, lines 8-12). Applicants respectfully request reconsideration and withdrawal of this rejection.

With regard to the first point, claims 3 and 9 have been amended and no longer call for the ranges of diameters to which the Examiner objected. With regard to the second point, it is not necessary for the practice of the claimed invention that one skilled in the art be able to distinguish type "A" cells from type "B" cells. With reference to Fig. 1, type "B" cells may be either proliferative or terminal. Both the terminal pathway, described at page 13, lines 21 to 24, and the proliferative pathway, described at page14, line 1 to page 15, line 25, may contain cells of type "A" and type "B." Without conceding that the specification does not enable one skilled in the art to distinguish type "A" and type "B" cells, this point is not germane to the enablement of the claimed invention.

Rejection of May 1, 2001, (C) as drawn to the classification of circulating cancer cells not arising from prostate or breast

At pages 6 to 7 of the Office Action dated May 1, 2001, the Examiner asserted that the specification would not have enabled one skilled in the art to practice the invention on types of cancer other than prostrate or breast cancers as one skilled in the art would be forced to identify cellular parameters which are indicative of other types of circulating cancer cells. (Page 7, lines 17-21). Applicants respectfully request reconsideration and withdrawal of this rejection.

In support of this rejection, the Examiner cites Ordonez (*Am. J. Surgical Pathology* 22:1215-1221, 1998) in support of the proposition that different types of cancers can be

differentiated on the basis of different staining for any given marker (e.g., cytokeratin), and concludes from this that it would require undue experimentation to practice the present methods on cancers other than breast and prostate. Applicants respectfully disagree.

The specification provides a broad teaching applicable to any form of cancer. In the specification starting at page 21 line 20 to page 29, line 25, a wide variety of markers that may be used to classify circulating cells are described. For example, determination of chromosomal abnormalities (page 28, line 18 *et seq.*), p53 expression (page 25, line 19 *et seq.*), and thymidylate synthetase activity (page 23, line 21 *et seq.*) would be applicable to various forms of cancer. Given the markers described in the specification, one of ordinary skill in the art could readily practice the methods of the present invention on any type of cancer. The Examiner is improperly attempting to limit the invention to the specific working examples provided. The art cited by the Examiner merely shows that those skilled in the art are well aware that different types of cancer express different markers and, thus, shows that determining an appropriate set of markers for any particular type of cancer is a routine practice in the art. In view of the routine nature of this practice, Applicants respectfully submit that one skilled in the art could make and use the presently claimed invention without undue experimentation. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this amendment and reply are respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

Claims 12, 14 18, and 20 have been canceled without prejudice or disclaimer.

The following claims have been amended.

1. (Twice amended) A method of classifying cancer cells in a body fluid sample of a patient with cancer or a patient suspected of having cancer, said method comprising: isolating circulating cancer cells [in the] from said body fluid sample of [the] said patient, and classifying said isolated cancer cells as terminal cells or proliferative cells by cytological and morphological analyses using fluorescence microscopy [characterizing said circulating cancer cells using cytological and morphological analyses by fluorescence microscopy to determine the classification of the cancer cells isolated, wherein the cancer cell classification comprises terminal cells and proliferative cells].

3. (Twice amended) The method of claim 2, wherein said terminal [cancer] cell is about 20-50 micrometers in diameter.

4. (Once amended) The method of claim 1, wherein at least one cancer cell is a terminal [cancer] cell that is a fragile, large cancer cell without a nucleus.

5. (Once amended) The method of claim 4, wherein said terminal [cancer] cell is about 20-40 micrometers in diameter.

6. (Twice amended) The method of claim 1, wherein at least one cancer cell is a terminal [cancer] cell with a nucleus.

8. (Once amended) The method of claim 1, wherein at least one cancer cell is a proliferative [cancer] cell.

10. (Once amended) The method of claim 8, wherein said cancer cell is a small proliferative [cancer] cell that is a dividing cell.

11. (Once amended) The method of claim 1, wherein at least three of said isolated cancer cells are in the form of a microtumor.

15. (Once amended) The method of claim 1[4], wherein said [natural] body fluid sample is blood.

19. (Twice amended) A method of determining the presence or absence of cancer cells capable of causing metastatic cancer, comprising:

(a) isolating circulating cancer cells in a body fluid sample of a patient with cancer or a patient suspected of having cancer;

(b) [characterizing said isolated cells using cytological and morphological analyses by fluorescence microscopy to distinguish cancer cell classes;

(c) determining the classification of the cancer cells isolated, wherein the cancer cell classification comprises terminal cells and proliferative cells; and

(d) wherein when said cells are classified as proliferative cells, they are capable of causing metastatic cancer] classifying said isolated cancer cells as terminal cells or proliferative cells by cytological and morphological analyses using fluorescence microscopy, thereby determining the presence or absence of cancer cells capable of causing metastatic cancer.

21. (Twice amended) A method of determining the efficacy of a medical procedure for treatment of cancer in a patient, said method comprising:

(a) conducting a first isolation of circulating cancer cells in a body fluid sample of [a] the patient[with cancer or a patient suspected of having cancer];

(b) classifying said isolated cancer cells as terminal cells or proliferative cells by [characterizing said isolated cells using] cytological and morphological analyses [by] using fluorescence microscopy [to distinguish cancer cell classes];

(c) [determining the classification of the cancer cells isolated, wherein the cancer cell classification comprises terminal cells and proliferative cells;

(d)] conducting a second isolation of circulating cancer cells in a body fluid sample of the patient;

(d) [(e)] repeating (b) on [the] said second isolated cancer cells [from the second isolation]; and

(e) comparing the number or classes of said first isolated cancer cells to the number or classes of said second isolated cancer cells,

[(f) repeating (c) on the cells from the second isolation;

(g) assessing whether a medical procedure is efficient based on the classification determined in (c) as compared to the classification determined in (f); and

(h)] wherein the first isolation is conducted before the administration of the medical procedure and the second isolation is conducted after the administration of the medical procedure, thereby determining the efficacy of said medical procedure.

23. (Once amended) The method of claim 21[2], wherein the presence of more terminal [cancer] cells in the second isolation than in the first isolation is indicative of a positive response to the medical procedure.

24. (Once amended) The method of claim 21[2], wherein the presence of more proliferative [circulating cancer] cells in the second isolation than in the first isolation is indicative of a negative response to the medical procedure.